Sexually Transmitted Infections

Editorials

Does brain penetration of anti-HIV drugs matter?

Soon after the introduction of protease inhibitors and the widespread use of combination antiretroviral therapy, the concept of eradication of HIV-1 from infected individuals seemed a realistic goal.[1] However, the possibility that sanctuaries for virus existed within anatomical sites, such as the central nervous system (CNS), that are protected from the peripheral immune response and that may have impaired drug penetration loomed as a major barrier to eradication. Today we are more cautious about the prospect of HIV-1 eradication. Yet consideration of protected viral reservoirs remains important, particularly in light of data that show different antiretroviral resistance mutations in viruses from brain compared with peripheral sites of infection.[2] Could the HIV epidemic be transformed into one in which systemic infection is controlled but brain infection, and dementia, persist? Could protected sites theoretically reinfect the blood and cause treatment failure, especially if they fostered local outgrowth of drug resistant virus? Many antiretrovirals, particularly the protease inhibitors, yield limited brain and cerebrospinal fluid (CSF) drug concentrations.[3] Are we thus allowing increased viral replication in the brain and potential treatment failure in our patients? To assess the importance of brain penetration of anti-HIV agents, several issues and questions must first be addressed. We conclude that until these issues are resolved antiretroviral regimens should be designed to include agents with good CNS penetration.

AIDS dementia is estimated to occur in about 15% of HIV-1 infected patients with advanced disease. The disorder is uncommon in the absence of significant immunosuppression and patients typically have peripheral blood CD4 cell counts below 200×10^6/l. The pathogenesis of AIDS dementia is incompletely understood, but is intimately linked to productive viral infection of brain macrophages or microglia; secondary mechanisms related to host factors as well as viral components probably play an important part.[4]

Cerebrospinal fluid viral content has been used as a surrogate for CNS infection.[5] Caution is needed, however, because HIV-1 in CSF may originate from blood, meninges, choroid plexus, or brain. With that caveat, studies have shown that HIV-1 can be identified in CSF from most infected individuals early in the course of disease. For example, Schacker and coworkers were able to culture virus from CSF from 12 of 24 HIV-1 seroconverters.[6] Similarly, Davis and coworkers were able to culture virus and amplify viral DNA from brain 15 days after accidental intravenous infection.[7] However, high levels of viral DNA are more common in brains from patients with AIDS than from asymptomatic HIV-1 infected individuals,[8] although levels of brain provirus are not necessarily higher in patients with dementia compared with patients with AIDS but no dementia.[9] Histopathological evidence of productive brain infection characterised by multinucleated giant cells is seen in some, but not all, patients with AIDS and is not seen in asymptomatic individuals.[8] Thus, despite early exposure of the CNS to virus, productive brain HIV-1 infection seems to occur late in the course of disease and does not develop in all individuals. These observations suggest that CNS virus infection may be controlled by local CNS host defence mechanisms during the asymptomatic phase of infection.

Productive brain infection late in the course of disease may occur by reinfection from the blood, by loss of local immune control of latent or low level viral replication, or by activation of latent or low level viral replication. If reinfection from blood is crucial, brain penetration of anti-HIV drugs is less important because control of blood virus will shield the brain from overwhelming infection. However, if loss of control or activation of infection occurs, adequate brain penetration of anti-HIV agents would be required to contain CNS infection.

Evidence in support of the hypothesis that brain infection occurs late and is caused by exposure from blood comes from studies of peripheral blood monocytes. Such studies have demonstrated that peripheral blood CD16 monocytes are more common in patients with dementia than in AIDS patients without dementia or in asymptomatic HIV-1 infected individuals.[10 11] These cells are latently infected with HIV-1 and virus can be co-cultured from them.[10] Conversely, proton magnetic resonance spectroscopic studies show subcortical metabolite abnormalities in neurologically asymptomatic HIV-1 infected individuals as well as in those with cognitive impairment.[12] These results argue against the concept of clearance of brain virus and subsequent late reinfection and for persistent low level brain infection throughout the course of HIV-1 disease, and suggest that CNS penetrating antiretroviral therapy will be necessary at all stages of disease.

Several studies directly or indirectly address the importance of CNS penetration of antiretroviral agents. We will start with the data from treatment, epidemiological, and necropsy studies that support the notion that CNS drug penetration does not matter but that shielding the CNS from infection is crucial. Based on animal (brain and CSF) and human (CSF) study of anti-HIV agents, didanosine (ddI) and zalcitabine (ddC) have poor CNS penetration.[3] None the less, addition of ddI or ddC to zidovudine (AZT) in the Delta trial was associated with a reduced risk of AIDS dementia compared with AZT monotherapy.[13] Similarly, in a study of subjects with AIDS enrolled in clinical trials of AZT and ddI, there was no difference in performance on neuropsychological tests between the treatment groups over 12 months of observation despite the fact that the ddI treated group had more advanced disease.[14] The incidence of AIDS dementia has decreased since the advent of potent antiretroviral regimens,[15] also suggesting that control of peripheral infection controls brain infection. However, the relative decline in incidence of AIDS dementia in the era of potent antiretroviral therapy may be less than for other AIDS defining illnesses,[15] thus tempering this conclusion (see below). None the less, differences in incidence of dementia between patients treated with regimens with good versus poor CNS penetration have not been explored. In a pathological study, continuous treatment with AZT or a switch from AZT to ddI were equally effective in preventing HIV encephalitis.[16]

Clinical and epidemiological studies can be cited in support of the hypothesis that adequate brain penetration of anti-HIV agents is required to treat CNS infection. Many of these studies are based on examination of CSF rather than brain. Thus, a brief digression is required to address the relation between CSF and brain HIV-1 infection.

Several studies support the contention that CSF HIV-1 RNA reflects brain infection in patients with advanced immunodeficiency (peripheral blood CD4 cell counts less than 200 $\times 10^6$/l) or clinically defined AIDS. For example, in a group of patients with very advanced disease, Cinque and coworkers showed that high levels of CSF HIV-1 RNA are significantly associated with histopathological evidence of HIV encephalitis.[17] Similarly, among patients with peripheral blood CD4 cell counts less than 200 $\times 10^6$/l, CSF HIV-1 RNA levels are significantly higher in patients with cognitive impairment[18] and progressively higher CSF levels are seen with increasing severity of dementia.[19 20] Moreover, Ellis and coworkers have shown that CSF HIV-1 RNA levels of 200 copies/ml or greater are associated with a significantly increased risk of development of cognitive impairment during 6–60 months of follow up.[21]

Like ddI and ddC discussed above, protease inhibitors (with the exception of indinavir) probably have poor CNS penetration.[3] Gisolf and coworkers recently reported that subjects treated with ritonavir and saquinavir without a nucleoside reverse transcriptase inhibitor were 42 times less likely to suppress CSF HIV-1 RNA below the level of detection at 12 weeks of therapy compared with those subjects who received the combination with a nucleoside agent.[22] In a preliminary analysis, one of us (CMM) has shown that subjects treated with potent antiretrovirals who did not experience a decline in CSF HIV-1 RNA after 8 weeks of treatment performed significantly worse on a brief neuropsychological test battery compared with those subjects with a decline in CSF HIV-1 RNA level.[23] These results suggest that failure to contain brain infection, as reflected in the CSF, may be manifested by worsening cognitive performance and they argue for the importance of using antiretroviral therapy that contains agents with good CNS penetration.

Two observations from epidemiological studies add further support to the contention that CNS drug penetration may be important. Firstly, as noted previously, the relative decline in AIDS dementia in the era of potent antiretroviral therapy may be less than for other AIDS defining illnesses.[15] Secondly, AIDS dementia is occurring in individuals with higher peripheral blood CD4 cell counts. In the same study, median peripheral blood CD4 cell count at diagnosis of AIDS dementia increased from 70 cells $\times 10^6$/l in 1992–5 to 170 cells $\times 10^6$/l in 1997,[15] supporting the contention that control of peripheral virus may not be sufficient to control brain infection.

These data raise several important questions. For example, even if brain reinfection occurs late in the course of HIV-1 disease and could be prevented by antiretroviral therapy that controls peripheral viral replication, is it possible to miss an early window of treatment opportunity for the CNS? Is there a point at which good peripheral viral treatment will be too late with respect to the CNS? Once infected, will brain virus begin to evolve independently of other compartments? Until these questions are definitively answered, clinicians must, whenever possible, use antiretroviral regimens that penetrate the CNS.

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